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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,660	11/28/2005	Gunther Harth	51326-00005 NAT	6518

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EXAMINER	
ISSAC, ROY P	

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
11/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,660	HARTH ET AL.	
	Examiner	Art Unit	
	Roy P. Issac	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,7,10-13,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,7, 10-13, 15-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/19/07 has been entered.

Applicants' amendment filed 10/19/07 wherein claims 1-2 have been cancelled is acknowledged. Claims 5, 7 and 10-16 are currently pending and are examined on the merits herein.

Rejections Withdrawn

In view of the cancellation of claims 1-2 and 14 all rejections made with respect to claims 1-2 and 14 in the previous office action are withdrawn.

The following is a new ground of rejection:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 7 10-13, and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,013,660 (Of Record) in view of Griffith et.al. (Methods in Enzymology, 143, 286-291; Of Record) further in view of Harth et. al. (Of Record).

The '660 patent is drawn to a method of for treating mammalian disease conditions associated with infection of pathogenic mycobacterium comprising the steps of administering L-methionine-S-sulfoxmine (MS) to a mammal in a dose sufficient to significantly inhibit the growth or survival of the pathogenic mycobacterium without harming said mammal. The '660 patent further claims the use of said compound for the treatment of several mycobacterium bacteria including, M.tuberculosis, and M.avium. The '660 patent further attributes the activity of MS and its analogs to their ability to inhibit the activity of the extracellular enzyme glutamine synthetase (GS) an extracellular protein which is essential for the growth of M. tuberculosis and other closely related pathogenic intracellular mycobacteria. Inhibition of the activity of M. tuberculosis glutamine synthetase, specifically that enzyme which is released extracellularly was found to inhibit the growth of M. tuberculosis cells resulting in the inhibition of bacterial growth. (Column 5, lines 50-61).

The '660 patent does not expressly disclose the particular alpha-alkylated sulfoxamines claimed herein.

Griffith OW teaches that α-ethylmethionine sulfoximine, one of the mycobacterial inhibitors of the present application as a selective inhibitor of glutamine synthetase. Griffith OW notes that, "Selective inhibition of either glutamine synthetase or γ-

glutamylcysteine synthetase is possible in vitro or in vivo using analogs of methionine sulfoximine. Thus, α-ethylmethionine sulfoximine inhibits only glutamine synthetase whereas prothionine sulfoximine inhibits only glutamine synthetase whereas porthionine sulfoximine, butathionine sulfoximine and higher S-alkyl analogs of methionine sulfoximine are specific inhibitors of γ-glutamylcysteine synthetase." (Page 287, Paragraph 1, lines 9-17).

Harth et. al. teaches that pathogenic Mycobacteria secrets large number of proteins in to extracellular milleu. One of the abundantly released proteins is the enzyme glutamine synthetase. However, nonpathogenic mycobacterial microorganisms do not release glutamine synthetase into the extracellular milleu. (Page 1425, Column 2, last paragraph and Page 1426, Column 1, first paragraph). Harth et. al. further teaches that the inhibition of enzyme glutamine synthetase blocks bacterial multiplication. (Page 1426, Column 1. Paragraph 3). Harth et. al. teaches that inhibition of extracellular glutamine synthetase blocks bacterial multiplication both in broth medium and in human mononuclear phagocytes and that growth inhibition is correlated with a marked reduction in the amount of virulence-associated cell wall component poly-L-glutamate/glutamine. (Page 1426, Column 1. Paragraph 3). Harth et. al. notes that; "Specifically, our study demonstrates that treatment of *M. tuberculosis* wiqth a drug that inactivates extracellular glutamine synthetase inhibits mycobacterial growth. Hence, drugs functionally analogous to L-methionine-S-sulfoximine, but perhaps with even greater specificity for *M. tuberculosis* enzyme relative to the mammalian enzyme have great potential as antibiotics against this pathogen." (Page 1434, Colunn 1, Pargraph

5, line 13 to Column 2, paragraph 1, lines 1-6). Harth et. al. further compared the sensitivity of glutamine synthetase inhibitors on purified *M. tuberculosis* glutamine synthetase to mammalian glutamine synthetase. (Page 1427, Column 1, Paragraph 2, lines 10-15). Harth et. al. further discloses the use of conventional antibiotics in combination with L-Methionine-S-Sulfoximine, in particular isoniazid. Harth et. al. notes that, "The most pronounced effect on bacterial growth was observed for isoniazid and rifampin at one-tenth their minimal inhibitory concentrations in combination with 0.2μM L-methionine-S-sulfoximine." The authors further notes that, "This result is consistent with the hypothesis that the inhibitory effect of L-methionine-S-sulfoximine on the extracellular glutamine synthase effects the integrity of the M-tuberculosis cell wall so as to allow antibiotics greater access to the bacterial cytoplasm." (Page 1433, Column 2, Paragraph 2, lines 1-23). Harth et. al. further teaches that, of the possible four racemic forms of the inhibitor (D, or L)-methionine-(S or R)-sulfoxamine, only L-methionine-S-sulfoximine is active against glutamine synthetase. (Page 1429, Column 1, Paragraph 2, lines 7-11). The disclosed concentratons of 0.2, 20 and 200μM inhibits mycobacterial growth and is considered an "anti-mycobacterial effective amount". The recitation, "wherein said composition effectively inhibits mycobacterial glutamine synthetase (MbGS), but does not substantially interfere with mammalian glutamine synthetase" is considered a functional description of an inherent property residing the administration of the same or substantially similar compounds for the treatment against the same bacterium.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use α-ethylmethionine sulfoximine as an inhibitor of mycobacterial glutamine synthetetase because, the '660 patent discloses L-methionine sulfoximine as a selective inhibitor of glutamine synthetase and Griffith teaches that α-ethylmethionine sulfoximine is a selective inhibitor of glutamine synthetase.

One having ordinary skill in the art would have been motivated employ particular alpha-alkylated compounds herein, because, '660 patent discloses suggests the use of analogues of methionine sulfoximine, and α-ethyl-methionine sulfoximine, the compound instantly claimed, is a well known analogue of methionine sulfoximine, known for its activity against glutamine synthetase. Furthermore, aklylated methionine sulfoximines are advantageous because of their reduced tendency to induce convulsions. As noted in MPEP 2144, "If such a species or subgenus is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties. See, e.g., Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also Deuel, 51 F.3d at 1558, 34 USPQ2d at 1214. The utility of such properties will normally provide some motivation to make the claimed species or subgenus. Id. Dillon, 919 F.2d at 697, 16 USPQ2d at 1904-05 (and cases cited therein). If the claimed invention and the structurally similar prior art species share any useful property, that will generally be sufficient to motivate an artisan of ordinary skill to make the claimed species, In fact, similar properties may normally be presumed when compounds are very close in

structure. Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also In re Grabiak, 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985) ("When chemical compounds have very close' structural similarities and similar utilities, without more a prima facie case may be made."). Thus, evidence of similar properties or evidence of any useful properties disclosed in the prior art that would be expected to be shared by the claimed invention weighs in favor of a conclusion that the claimed invention would have been obvious. Dillon, 919 F.2d at 697-98, 16 USPQ2d at 1905; In re Wilder, 563 F.2d 457, 461, 195 USPQ 426, 430 (CCPA 1977); In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

As such, one of ordinary skill in the art would have had reasonably expected that alpha-alkyl-methionine-sulfoximine alone or in combination with another agent such as isoniazid would also have anti-mycobacterial properties.

Thus, the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 5, 7, 10-13 and 15-16 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,013,660 in view of Griffith OW et. al (J. Biol. Chem. 1979, 1205-1210; Of Record).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the '660 patent is drawn to a method of for treating mammalian disease conditions associated with infection of pathogenic mycobacterium comprising the steps of administering L-methionine-S-sulfoxmine (MS) to a mammal in a dose sufficient to significantly inhibit the growth or survival of the pathogenic mycobacterium without harming said mammal. The '660 patent further claims the use of said compound for the treatment of several mycobacterium bacteria including, M.tuberculosis, and M.avium. The '660 patent further attributes the activity of MS and its analogs to their ability to inhibit the activity of the extracellular enzyme glutamine synthetase (GS) an extracellular protein which is essential for the growth of M. tuberculosis and other closely related pathogenic intracellular mycobacteria. Inhibition of the activity of M. tuberculosis glutamine synthetase, specifically that enzyme which is

released extracellularly was found to inhibit the growth of M. tuberculosis cells resulting in the inhibition of bacterial growth. (Column 5, lines 50-61).

The claims of the instant application is drawn to compositions including alpha-alkylated methionine sulfoximines and methods of treating pathogenic mycobacterial infections using said compounds.

The '660 patent does not expressly disclose alpha alkylated L-methionine-S-sulfoximine or a racemic mixture of the same or other alpha alkylated butyrates for the treatment of pathogenic mycobacterium infection.

Griffith et. al. discloses the use of alpha-alkylated analogs of methionine sulfoximine, in particular alpha-ethyl-methionine sulfoximine for the selective inhibition of glutamine synthetase. (Page 2333, Abstract). Methionine sulfoximine is a known convulsant. (Page 2333, Column 1, Paragraph 2, lines 1-5). Griffith et. al. discloses that while methionine sulfoximine induces convulsions at a dosage of 1mmol/kg, alkylated methionine sulfoximines, in particular alpha-ethyl-methionine sulfoximines only produced convulsions at a much higher dosage. (Page 2335, Column 2, Paragraph 4, and Page 2336, Column 2, Paragraph 1). One of ordinary skill in the art would have reasonably expected that the instant compound, would have same or substantially similar beneficial therapeutic effects and usefulness in methods for treating, palliating or inhibiting mycobacterial infections in a mammal, based on the reasonable expectation that structurally similar species usually have similar properties. Herein, the branched and straight chain C1-C8 alkyl at R1 is considered structurally similar to the prior art compounds with methyl and ethyl groups at the R1 position. As noted in MPEP 2144,

"If such a species or subgenus is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties. See, e.g., Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also Deuel, 51 F.3d at 1558, 34 USPQ2d at 1214. The utility of such properties will normally provide some motivation to make the claimed species or subgenus. Id. Dillon, 919 F.2d at 697, 16 USPQ2d at 1904-05 (and cases cited therein). If the claimed invention and the structurally similar prior art species share any useful property, that will generally be sufficient to motivate an artisan of ordinary skill to make the claimed species, In fact, similar properties may normally be presumed when compounds are very close in structure. Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also In re Grabiak, 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985) ("When chemical compounds have very close' structural similarities and similar utilities, without more a prima facie case may be made."). Thus, evidence of similar properties or evidence of any useful properties disclosed in the prior art that would be expected to be shared by the claimed invention weighs in favor of a conclusion that the claimed invention would have been obvious. Dillon, 919 F.2d at 697-98, 16 USPQ2d at 1905; In re Wilder, 563 F.2d 457, 461, 195 USPQ 426, 430 (CCPA 1977); In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Furthermore, a substantial number of the compounds encompassed by the generic formula I is considered homologs of the L-methionine-S-sulfoximine claimed in the '660 patent and the alkyl analogs of methionine sulfoximine disclosed in Griffith et. al. The members of a

homologous series must possess unexpected properties not possessed by the homologous compounds disclosed in the prior art. *In re Hass* 141 F.2d 127, 60 USPQ 548 (CCPA 1944). Adjacent homologs are considered to obvious absent unexpected results. *In re Henze* 85 USPQ 261, 263 (CCPA 1950).

One of ordinary skill in the art at the time the invention was made would have been motivated to employ alpha-alkylated methionine sulfoximines to treat mycobacterial infections because alpha-alkylated methionine sulfoximines were well known for their selective inhibition of glutamine synthetase and the '660 patent shows that the inhibition of glutamine synthetase by methionine sulfoximine leads to the inhibition of mycobacterial growth. Furthermore, aklylated methionine sulfoximines are advantageous because of their reduced tendency to induce convulsions.

Response to Arguments

Applicant's arguments filed 10/19/07 have been fully considered but they are not persuasive. Applicants argue that, claim 1 of the '660 patent only disclose L-methionine-S-sulfoximine and the disclosure of the secondary reference (Griffith) cannot broaden the scope of claim 1 of the '660 patent. This argument was found unpersuasive since the compounds disclosed in the secondary reference are considered to have strong structural similarity with the sulfoximine compound claimed in the '660 patent as discussed above. Arguments directed to individual references are not persuasive where the rejection is based on the combined teachings of the

references. *In re Young* , 403 F.2d 754, 159 USPQ 725 (CCPA 1968). The double patenting rejection is still deemed proper and is adhered to.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 7 10-13, and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harth et.al. (J.Exp. Med. 189(9), 1425-1435, 1999; Of Record) in view of Griffith et.al. (Methods in Enzymology, 143, 286-291; Of Record).

Harth et. al. teaches that pathogenic Mycobacteria secrets large number of proteins in to extracellular milleu. One of the abundantly released proteins is the enzyme glutamine synthetase. However, nonpathogenic mycobacterial microorganisms do not release glutamine synthetase into the extracellular milleu. (Page 1425, Column 2, last paragraph and Page 1426, Column 1, first paragraph). Harth et. al. further teaches that the inhibition of enzyme glutamine synthetase blocks bacterial multiplication. (Page 1426, Column 1. Paragraph 3). Harth et. al. teaches that inhibition of extracellular glutamine synthetase blocks bacterial multiplication both in broth medium and in human mononuclear phagocytes and that growth inhibition is correlated with a marked reduction in the amount of virulence-associated cell wall component poly-L-glutamate/glutamine. (Page 1426, Column 1. Paragraph 3). Harth et. al. notes that;

"Specifically, our study demonstrates that treatment of *M. tuberculosis* wiqth a drug that inactivates extracellular glutamine synthetase inhibits mycobacterial growth. Hence, drugs functionally analogous to L-methionine-S-sulfoximine, but perhaps with even greater specificity for *M. tuberculosis* enzyme relative to the mammalian enzyme have great potential as antibiotics against this pathogen." (Page 1434, Colunn 1, Pargraph 5, line 13 to Column 2, paragraph 1, lines 1-6). Harth et. al. further compared the sensitivity of glutamine synthetase inhibitors on purified *M. tuberculosis* glutamine synthetase to mammalian glutamine synthetase. (Page 1427, Column 1, Paragraph 2, lines 10-15). Harth et. al. further discloses the use of conventional antibiotics in combination with L-Methionine-S-Sulfoximine, in particular isoniazid. Harth et. al. notes that, "The most pronounced effect on bacterial growth was observed for isoniazid and rifampin at one-tenth their minimal inhibitory concentrations in combination with 0.2μM L-methionine-S-sulfoximine." The authors further notes that, "This result is consistent with the hypothesis that the inhibitory effect of L-methionine-S-sulfoximine on the extracellular glutamine synthase effects the integrity of the M-tuberculosis cell wall so as to allow antibiotics greater access to the bacterial cytoplasm." (Page 1433, Column 2, Paragraph 2, lines 1-23). Harth et. al. further teaches that, of the possible four racemic forms of the inhibitor (D, or L)-methionine-(S or R)-sulfoxamine, only L-methionine-S-sulfoximine is active against glutamine synthetase. (Page 1429, Column 1, Paragraph 2, lines 7-11). The disclosed concentratons of 0.2, 20 and 200μM inhibits mycobacterial growth and is considered an "anti-mycobacterial effective amount". The recitation, "wherein said composition effectively inhibits mycobacterial glutamine synthetase

(MbGS), but does not substantially interfere with mammalian glutamine synthetase" is considered a functional description of an inherent property residing the administration of the same or substantially similar compounds for the treatment against the same bacterium.

Harth et. al. does not expressly disclose the use of the particular α-alkylated compounds of formula I with methyl or ethyl substitution at the R-1 position for inhibiting, treating or palliating mycobacterial infections; in particular Harth et. al. does not disclose the use of alpha-methyl-(D or L)-methionine-(S or R)- sulfoxamine or alpha-methyl-L-methionine-S-sulfoxamine or alpha-ethyl-(D or L)-methionine-(S or R) -sulfoxamine or alpha-ethyl-L –methionine-S-sulfoxamine as anti-mycobacterial agents.

Griffith OW teaches that α-ethylmethionine sulfoximine, one of the mycobacterial inhibitors of the present application as a selective inhibitor of glutamine synthetase. Griffith OW notes that, "Selective inhibition of either glutamine synthetase or γ-glutamylcysteine synthetase is possible in vitro or in vivo using analogs of methionine sulfoximine. Thus, α-ethylmethionine sulfoximine inhibits only glutamine synthetase whereas prothionine sulfoximine inhibits only glutamine synthetase whereas porthionine sulfoximine, butathionine sulfoximine and higher S-alkyl analogs of methionine sulfoximine are specific inhibitors of γ-glutamylcysteine synthetase." (Page 287, Paragraph 1, lines 9-17).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use α-ethylmethionine sulfoximine as an inhibitor of mycobacterial glutamine synthetetase because, Griffith teaches that α-ethylmethionine

sulfoximine is a selective inhibitor of glutamine synthetase and Harth et. al. teaches that the growth of pathogenic mycobacteria can be inhibited by the inhibition of glutamine synthetase, in particular analogues of methionine sulfoximine.

One having ordinary skill in the art would have been motivated employ particular alpha-alkylated compounds herein, because, Harth et. al. suggests the use of analogues of methionine sulfoximine, and α-ethyl-methionine sulfoximine, the compound instantly claimed, is a well known analogue of methionine sulfoximine, known for its activity against glutamine synthetase. Furthermore, aklylated methionine sulfoximines are advantageous because of their reduced tendency to induce convulsions.

As noted in MPEP 2144, "If such a species or subgenus is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties. See, e.g., Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also Deuel, 51 F.3d at 1558, 34 USPQ2d at 1214. The utility of such properties will normally provide some motivation to make the claimed species or subgenus. Id. Dillon, 919 F.2d at 697, 16 USPQ2d at 1904-05 (and cases cited therein). If the claimed invention and the structurally similar prior art species share any useful property, that will generally be sufficient to motivate an artisan of ordinary skill to make the claimed species, In fact, similar properties may normally be presumed when compounds are very close in structure. Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also In re Grabiak, 769 F.2d 729, 731, 226 USPQ 870,

871 (Fed. Cir. 1985) ("When chemical compounds have very close' structural similarities and similar utilities, without more a prima facie case may be made."). Thus, evidence of similar properties or evidence of any useful properties disclosed in the prior art that would be expected to be shared by the claimed invention weighs in favor of a conclusion that the claimed invention would have been obvious. Dillon, 919 F.2d at 697-98, 16 USPQ2d at 1905; In re Wilder, 563 F.2d 457, 461, 195 USPQ 426, 430 (CCPA 1977); In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

As such, one of ordinary skill in the art would have had reasonably expected that alpha-alkyl-methionine-sulfoximine would also have anti-mycobacterial properties.

Thus, the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 10/19/07 have been fully considered but they are not persuasive. Applicants argue that, the glutamine synthetase used in Griffith et al. is a mammalian GS which is a different protein than mycobacterial GS. This argument was found unpersuasive since claims in the '660 patent were drawn to a method of for treating mammalian disease conditions associated with infection of pathogenic mycobacterium comprising the steps of administering L-methionine-S-sulfoxmine (MS) to a mammal in a dose sufficient to significantly inhibit the growth or survival of the pathogenic mycobacterium without harming said mammal. The selective inhibition of mycorbacterium by L-methionine-S-sulfoximine is claimed in the '660 patent and the

instant claims are directed to the selective inhibition of mycobacterial infection in mammal comprising compounds with strong structural similarity to L-methionine-S-sulfoximine. Applicants further argue that until the instant invention, it was not known if these claimed compounds would exhibit inhibition of mycobacterial GS to a degree sufficiently greater than their inhibition of mammalian GS. However, Harth et. al. teaches that inhibition of extracellular glutamine synthetase blocks bacterial multiplication both in broth medium and in human mononuclear phagocytes. The claims herein is directed to the treatment of mycobacterial infections in mammals comprising the administration of compounds with substantially similar structure as those described in Harth et. al. and the particular compounds claimed herein were already known in the prior art as disclosed by Griffith et. al. Herein structurally similar compounds were well known for their activity against mycobacterial infection and the alpha alkylated compounds were well known in the prior art, also known to have activity against mammalian glutamine synthetase. As such, one of ordinary skill in the art would have had reasonably expected that alpha-alkyl-methionine-sulfoximine would also have anti-mycobacterial properties. Applicants further argue that Griffith et. al. at the time of the invention it was not known if the established inhibitors of mammalian GS would also inhibit mycobacterial GS. However, the rejection herein are based on structural similarity of established anti-mycobacterial agents. At the time of the invention, it was well known that L-methionine-S-sulfoximine was a potent anti-mycobacterial agent, and that compounds with similar structure exhibited activity against mammalian GS. In response to applicant's arguments against the references individually, one cannot show

nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Harth et. al. disclosed L-methionine-S-sulfoximine as an anti-mycobacterial agent and Griffith et. al.disclosed structurally similar alpha-alkyl-methionine-sulfoximine compounds with activity against mammalian GS. As such, the claimed invention herein is prima facie obvious over the combined teachings of the prior art. For the above reasons claims 5, 7 10-13, and 15-16 are considered properly rejected under 35 USC 103(a) and is adhered to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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